REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow claims 15-20, 26-28, and 30-47, the only claims pending and currently under examination in this application.

Claims 15, 30, and 39 have been amended. Support for the amendments can be found in the claims as originally filed and throughout the specification at, for example, claim 15: page 14, paragraphs [0064] to [0066], and paragraph [00134] bridging pages 31 and 32; claim 30: page 14, paragraphs [0064] to [0066], and paragraph [00134] bridging pages 31 and 32; and claim 39: page 14, paragraphs [0064] to [0066], and paragraph [00134] bridging pages 31 and 32.

The specification has been amended to address the Examiner's objections regarding SEQ ID NOs and the referenced reissue patent. The specification has also been amended to clarify the description of original Figure 2B as suggested by the Examiner.

No new matter is added.

Accordingly, the Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Rejections and objections of Office Action dated May 19, 2004

The Applicants acknowledge with gratitude the Examiner's indication that the objections to the specification, and rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102, as set forth in the Office Action dated May 19, 2004 have been withdrawn.

Compliance with Sequence Listing

Enclosed with this response please find a substitute copy of the sequence listing in both paper and computer readable form. Above please find an amendment

requesting its entry into the present application, in place of all previously filed sequence listings.

I hereby certify that the enclosed substitute Sequence Listing is being submitted under 37 CFR §§ 1.821(c) and (e) in paper and computer readable form (Compact Disk labeled 'CRF').

As required by 37 CFR 1.821(f), I hereby state that the content of the paper and computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e) are the same. The Computer Readable Format (CRF), being submitted under 37 CFR §§ 1.52(e) and 1.824, is formatted on IBM-PC, the operating system compatibility is MS-Windows and the file listing is:

Sequence Listing.txt 13.4 KB created June 16, 2005.

Objections to the Specification

Compliance with Sequence Rules (Office Action, page 3)

The Office Action notes the following objections to the sequence listing filed on November 24, 2004:

- Claim 15 discloses sequences without the benefit of a SEQ ID NOs.
- Claim 30 discloses sequences without the benefit of a SEQ ID NOs.
- Claim 39 discloses sequences without the benefit of a SEQ ID NOs.

It is believed the above amendments to the claims to incorporate SEQ ID NOs and the new sequence listing provided herewith address all of the Examiner's objections.

Drawings (Office Action, page 3)

The Office Action has maintained the objection to Figure 2B. The Examiner has indicated that the replacement Figure 2B submitted with the response filed on August 19, 2004 has not been entered because the Figure remains unclear. The Examiner also

suggests using original Figure 2B and amending the brief description of the drawing in to include SEQ ID NOs by virtue of nucleotide location. In view of the amendments to the specification to include SEQ ID NOs, this rejection may be withdrawn.

Specification (Office Action, page 4)

The Office Action has objected to the specification for containing a reference to "U.S. RE 30,985" in paragraph [00102]. In particular, the Office Action asserts the reference is confusing. The specification has been amended for clarity to recite "U.S. Reissue Patent No. RE30,986". In view of the amendment, this rejection may be withdrawn.

35 U.S.C. § 112, second paragraph

The Office Action has maintained the rejection of claims 30-38 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The rejection has also been amended to include claims 15-20, 26-28, and 39-47.

In particular, the Examiner states that "the mere iteration of NH2 or COOH, particularly in the absence of SEQ ID NO's, does not define the metal affinity peptides as N or C terminus peptides" (Office Action, page 5). However the applicants respectfully disagree.

The specification clearly provides that the use of the terms "NH2" and "COOH" refers to amino acids present at the amino or carboxy terminus of a polypeptide. For example, the specification, on page 10, paragraph [0046] specifically states the following with respect to the objectionable terms:

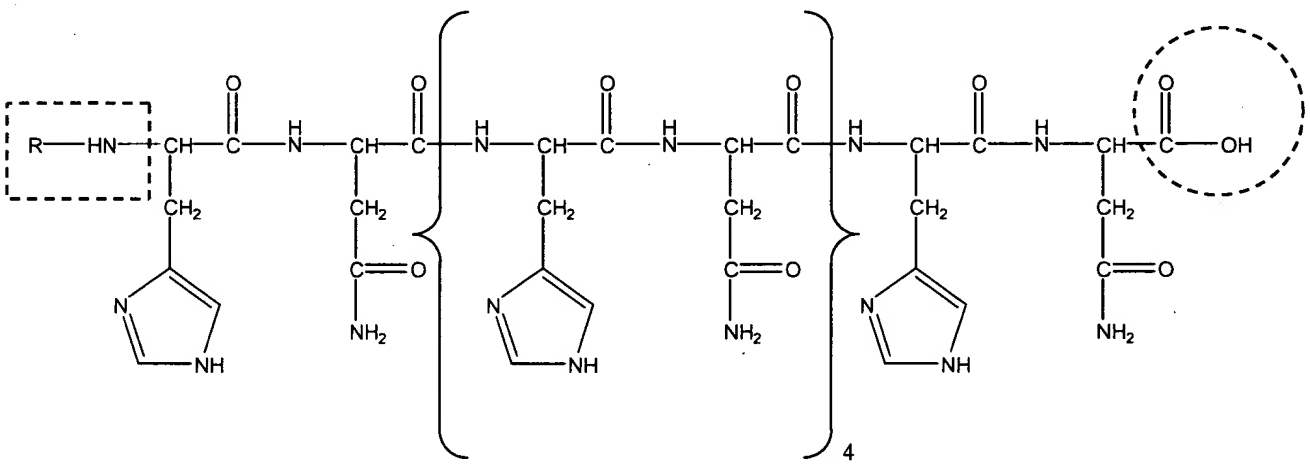
> **NH_2 refers to the free amino group** present at the **amino terminus** of a polypeptide. **COOH refers to the free carboxyl group** present at the **carboxyl terminus** of a polypeptide.

(emphasis added).

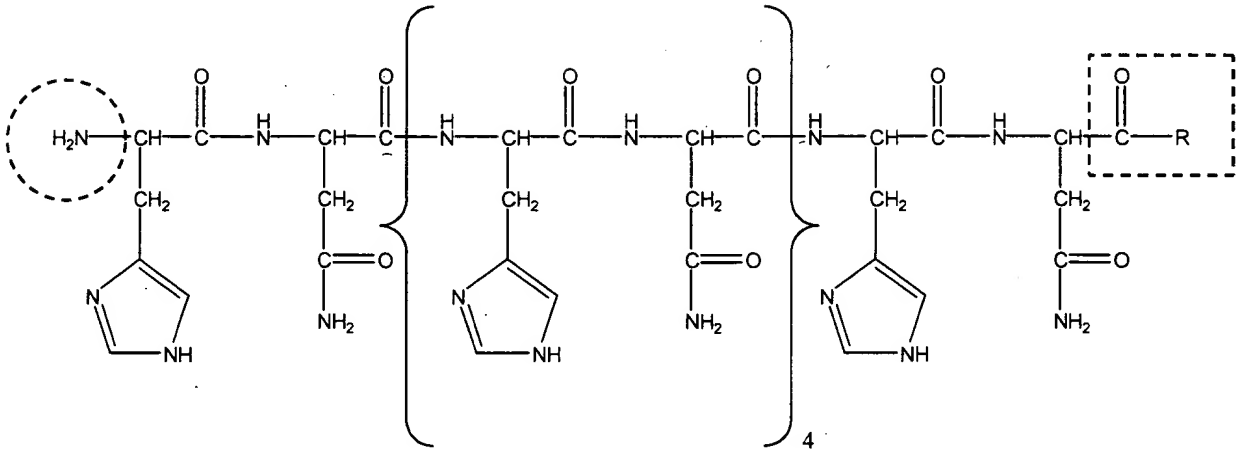
The Office Action also indicates that "'NH_2-(His-Asn)$_n$' is an equivalent peptide to '(His-Asn)$_n$-COOH' by virtue of peptide residue nomenclature wherein every residue has an NH2 group and has a COOH group" (Office Action, page 5). However, the Applicants respectfully disagree.

As demonstrated by the chemical structures below, an NH_2 group or a COOH group is only present at either a free amino terminus or a free carboxyl terminus, respectively (represented in the structures below using dashed circles). When the carboxyl or amino terminus of the peptide is fused to an additional amino acid sequence, **there is not an NH_2 group or a COOH group, but instead a NH group or a CO group** (represented in the structures below using dashed rectangles). Therefore every residue does not have a terminal NH2 group or has a COOH group as indicated in the Office Action.

Structure 1: (His-Asn)$_n$-COOH



Structure 2: NH_2-(His-Asn)$_n$



Accordingly, in view of the remarks made above, the Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 101

The Office Action has maintained the rejection of claims 15 and 17-20 under 35 U.S.C. § 101 as allegedly claiming non-statutory subject matter, and has amended the rejection to include claims 29-37. In particular, the Office Action maintains that claims 15, 30, and 39 do not sufficiently distinguish over polynucleotides as they naturally exist. This rejection is respectfully traversed.

Claims 15, 30, and 39 have been amended to recite "An isolated polynucleotide" as suggested in the Office Action. Therefore, the Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 102

Hirota et al. (Office Action, Page 7)

The Office Action has maintained the rejection of Claims 30-33 under 35 U.S.C. § 102(b) as allegedly being anticipated by Hirota et al., 1990 Nuc. Acid Res., 18:21 (hereinafter Hirota et al.). This rejection is respectfully traversed.

In maintaining the rejection, the Office Action indicates that the "inclusion of NH2- and –COOH does not particularly indicate that the tag must be on the terminus. The Applicants respectfully disagree. As noted in greater detail above, use of the terms "NH2" and "COOH" refers to amino acids present at the amino or carboxy terminus of a polypeptide. For example, the specification, on page 10, paragraph [0046] specifically states the following with respect to the objectionable terms:

> **NH_2 refers to the free amino group** present at the **amino terminus** of a polypeptide. **COOH refers to the free carboxyl group** present at the **carboxyl terminus** of a polypeptide.

(emphasis added).

In contrast to the present invention, Hirota et al. discloses a nucleic acid molecule that includes **an internal** His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn fragment. Nowhere does Hirota et al. disclose that the fragment may be located **at the N- or C-terminus of a polypeptide, fused to an amino- or carboxy-terminal amino acid**. Such is simply not disclosed in the cited reference.

Accordingly, the cited reference fails to disclose a His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn **fused to an amino- or carboxy-terminal amino acid**. Since the cited reference does not teach each and every limitation found in the claim, the cited reference fails to anticipate claims 30-33. Therefore, the Applicants respectfully request that this rejection be withdrawn.

CLONTECHniques, July 1998 (Office Action, Page 7)

The Office Action has maintained the rejection of claims 30-34 and 36-38 under 35 U.S.C. § 102(a) as allegedly being anticipated by CLONTECHniques (HAT™ Protein Expression & Purification System, July 1998) (Hereinafter "CLONTECHniques, July 1998"). This rejection is respectfully traversed.

In maintaining the rejection, the Office Action states that the declaration filed on August 19, 2004 under 37 C.F.R. § 1.131 is ineffective to overcome the cited reference. In particular, the Office Action states that the "evidence that Applicants had conceived of

the invention prior to July 1998...does not teach the claimed invention...[t]he description in the Form clearly teaches residues 1-32 of the chicken LDH sequence as an affinity tag and not resides 6-21 of said sequence as claimed" (Office Action, page 8). In response, the Applicants enclose herewith a revised Declaration under 37 C.F.R. §1.131.

The enclosed revised Declaration under 37 C.F.R. §1.131 demonstrates that the claimed subject matter of the present application was invented by the inventors prior to the cited reference. In particular, the revised declaration demonstrates that the claimed subject matter of His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn was invented by the inventors prior to July 1998.

> As set forth in 37 C.F.R. §1.131:
>
> (a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§1.42, 1.43, or 1.47, ***may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference*** or activity on which the rejection is based. . . .
>
> (b) ***The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference***, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. . . . (emphasis added)

As such, a 35 U.S.C. §102(a) rejection may be withdrawn if the Applicants can establish, by means of a declaration and a showing of facts, that the claimed subject matter was invented prior to the effective date of the cited reference.

In order to establish that the claimed invention was invented prior to the July 1998 priority date of the cited reference, the Applicants submit herewith the Declaration of Grigoriy S. Tchaga and George G. Jokhadze under 37 C.F.R. §1.131. This declaration provides a showing of facts that the inventors invented the claimed invention prior to the July 1998 effective priority date of the cited reference in that the inventors had invented compositions and methods of incorporating a polyhistidine metal ion affinity sequence at the N-or C-terminal sequence of recombinant proteins for the

purification of the recombinant proteins prior to the effective date of July 1998 of the cited reference.

Specifically, the declaration provides a series of laboratory notebook pages which describe incorporation of a polyhistidine metal ion affinity sequences at the N-terminal sequence of a recombinant protein and use of the affinity sequence for the purification of the recombinant protein with high selectivity.

Page 1 of Exhibit A briefly describes the purification protocol for the HAT-DHFR using FPLC under native conditions and also by batch-gravity flow under denaturing conditions. Page 2 of Exhibit A shows preliminary purification results for the HAT-DHFR. Page 3 of Exhibit A is a letter from ATG Laboratories, the contract laboratory employed to clone the HAT-DHFR fusion polypeptide. The letter described in detail the procedure used for cloning the DHFR gene into the KpnI site of the pHS20 vector in order to generate the HAT-DHFR fusion polypeptide. Page 4 of Exhibit A provides the N-terminal portion of the nucleic acid and amino acid sequence of the HAT-DHFR fusion protein encoded vector generated by ATG Laboratories. The amino acid sequence of the metal ion affinity tag is shown in the last two rows and is highlighted and shown in reverse order.

Since the Applicants have provided a declaration and facts that show invention prior to the effective date of the cited reference, the rejection of claims 30-34 and 36-38 under 35 U.S.C. §102(a) may be withdrawn.

Sato et al. (Office Action, Page 8)

The Office Action has maintained the rejection of Claims 39-44 under 35 U.S.C. §102(e) as allegedly being anticipated by Sato et al. (U.S. Patent Application 2003/0079237). This rejection is respectfully traversed.

In maintaining the rejection, the Office Action states that "the language of the Claim 39 does not limit the scope to N or C-terminal peptides" (Office Action, page 8). The Applicants respectfully disagree. As noted in greater detail above, use of the terms "NH2" and "COOH" refers to amino acids present at the amino or carboxy terminus of a

polypeptide. For example, the specification, on page 10, paragraph [0046] specifically states the following with respect to the objectionable terms:

> **NH_2 refers to the free amino group** present at the **amino terminus** of a polypeptide. **COOH refers to the free carboxyl group** present at the **carboxyl terminus** of a polypeptide.
>
> (emphasis added).

In contrast to the present invention, Sato et al. discloses a nucleic acid molecule that includes **an internal** His-Asn-His-Asn-His-Asn fragment. Nowhere does Sato et al. disclose that the fragment may be located **at the N- or C-terminus of a polypeptide, fused to an amino- or carboxy-terminal amino acid**. Such is simply not disclosed in the cited reference.

Accordingly, the cited reference fails to disclose a His-Asn-His-Asn-His-Asn **fused to an amino- or carboxy-terminal amino acid**. Since the cited reference does not teach each and every limitation found in the claim, the cited reference fails to anticipate claims 39-44. Therefore, the Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: 7.11.05

By: _____
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